REMARKS

Claims 1-52 are pending in the application prior to entry of amendments submitted herewith. Claims 20-23, 25, 26, 35 and 37-46 are withdrawn from consideration. Claims 1-19, 24, 27-34, 36 and 47-52 have been examined, and Claims 1-19, 24, 27-34, 26, 47 and 49-52 stand rejected. Claim 48 has been objected to only as depending from a rejected claim. By amendment herewith, Claims 1, 7, 11, 14, 15, 16, 27-29, 31, 32 and 48 are being changed, Claim 51 is being cancelled and new Claims 53-84 are being added.

Claim 48 has been placed in independent form, and the objection to that claim as depending from a rejected base claim should be withdrawn and the claim should be allowed, along with new Claims 53-84 that depend directly or indirectly from Claim 48.

Each of the specific issues raised by the Examiner in the June 4, 2003, Office Action is addressed below.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 29 and 31 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter Applicant regards as the invention. Claim 29 was objected to because it "contains an improper Markush group". It is respectfully noted that Markush-type language is only one possible way of expressing alternative limitations (See, MPEP § 2173.05(h)). There is nothing unclear or indefinite about the expression of alternative limitations in Claim 29. Nevertheless, Claim 29 has been amended to include introductory text for alternative limitations of the type used in *Ex Parte* Markush, 1925 C.D. 126 (Comm'r Pat 1925). This amendment is being made solely to accommodate the Examiner's textual preference, and not for any reason relating to patentability. The Examiner specifically objected to Claim 31 by asserting insufficient antecedent basis for the limitation "wherein the pycocolloid comprises agar". To obviate the objection, Claim 31 has been amended to refer to "second biocompatible polymer" rather than "pycocolloid". The rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

Rejection Under 35 U.S.C. § 103(a),
Based on Stratton et al. and Gentz et al.

The Examiner has rejected Claims 1, 4-13, 15-19, 24, 27-34, 36 and 49-52 under 35 U.S.C. § 103(a) citing to Stratton et al (U.S. Patent No. 5,861,174) in view of Gentz et al. (U.S. Patent No. 6,238,888). The rejection is traversed.

Claim 1, as amended herewith, is directed to a hematopoietic growth factor delivery composition, and requires a specific combination of components and composition formulation properties, and in particular, the claimed hematopoietic growth factor delivery composition includes a hematopoietic growth factor, a first biocompatible polymer, a liquid vehicle, and a second biocompatible polymer, with the first biocompatible polymer interacting with the liquid vehicle to impart reverse thermal viscosity behavior to the composition, with the second biocompatible polymer being a protective colloid inhibiting dissolution into aqueous liquids of the first biocompatible polymer at least when the composition is in a higher viscosity form, and with specific compositional ranges of from 60 weight percent to 96 weight percent for the liquid vehicle, from 5 weight percent to 33 weight percent for the first biocompatible polymer and from 0.1 weight percent to 5 weight percent for the second biocompatible polymer. This application was subject to species restriction with respect to the first biocompatible polymer, the second biocompatible polymer and the hematopoietic growth factor. Elected species are hydroxypropylmethyl cellulose (HPMC) for the second biocompatible polymer, G-CSF for the hematopoietic growth factor, and polymers containing polyoxypropylene for the first biocompatible polymer.

The Examiner cites to Stratton et al. as disclosing compositions for delivery of pharmacologically active proteins comprising polyoxyethylene-polyoxypropylene polymers, with examples of polypeptides suitable for incorporation in the delivery system including colony-stimulating factors. The Examiner specifically notes that Stratton et al. do not teach the second biocompatible polymer or the specific viscosity properties of the claimed invention. The Examiner then cites to Gentz et al. as teaching a pharmaceutical formulation comprising Keratinocyte Growth Factor-2 polypeptide, a buffer and polyoxyethylene-polyoxypropylene block copolymer and HPMC.

It is respectfully submitted that (1) the teachings of Stratton et al. and Gentz et al. are not combinable as suggested by the Examiner to make obvious the invention recited in Claim 1 and

(2) even if the references were combinable, the combination still would not disclose or suggest the claimed invention, as discussed below.

There is no teaching, motivation or suggestion identifiable in either of Stratton et al. or Gentz et al. that would lead one of ordinary skill in the art to combine the teaching of the two references. The teachings of Stratton et al. are directed to a delivery system made with a polyoxyethylene-polyoxypropylene block copolymer formulated for gelling, which delivery composition is asserted by Stratton et al. to be generally applicable for suspensions of macromolecular polypeptides. (See, Stratton et al., for example, at column 1, lines 7-12, column 3 lines 64-67 and column 4, lines 63 through column 5, line 19.) Stratton et al. provide specific working examples with different macromolecular polypeptides, including chymotrypsin (Example 1), subtilisin (Example 2), lactate dehydrogenase (Example 3), bovine serum albumin (Example 4) and insulin (Example 5). At column 5, lines 46-60, Stratton et al. also present lists of exemplary classes and specific examples of macromolecular polypeptides for potential incorporation in the general delivery system, which as noted by the Examiner include "colony-stimulating factors". Stratton et al., however, provide no discussion in relation to any special formulation considerations for such colony-stimulating factors, consistent with the disclosure by Stratton et al. that the delivery system is generally applicable for macromolecular polypeptides generally. Because the delivery system is disclosed as applicable generally for macromolecular polypeptides, Stratton et al. understandably provide no discussion concerning varying from the disclosed delivery system, which would be inconsistent with the asserted general applicability of the delivery system.

In contrast to the teachings of Stratton et al., the teachings of Gentz et al. are narrowly focused on formulations specifically for delivery of Keratinocyte Growth Factor-2 and deletion or point or substitution mutants thereof, referred to by Gentz et al. as "KGF-2 polypeptides" (See, Gentz et al., for example, at column 1, lines 12-17 and column 2, lines 2-8). Gentz et al. do not even discuss delivery compositions including hematopoietic growth factors or any special considerations for delivery of hematopoietic growth factors. There is no reason why one of ordinary skill in the art would consider the teachings of Gentz et al. (which are narrowly focused specifically on KGF-2 polypeptides) in combination with the teachings of Stratton et al. (which concern a delivery system asserted to be generally applicable for suspensions of macromolecular polypeptides) with respect to delivery specifically of hematopoietic growth factors (which is the

subject of the pending claims). The present invention is concerned specifically with delivery compositions for hematopoietic growth factors, not KGF-2 polypeptides, and the Examiner has provided no reasoning why one of ordinary skill in the art would even consider Gentz et al. specifically in relation to delivery of hematopoietic growth factors, let alone in combination with Stratton et al. Concerning teaching, suggestion or motivation for combining the references, the Examiner makes only the following statement:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Stratton et al. and Gentz et al. to make the instant composition. The motivation and expected success is provided by both Stratton and Gentz. Stratton et al. teach the use of polyoxyethylene-polyoxypropylene block copolymers for sustained release delivery systems. Polyoxyethylene-polyoxypropylene block copolymers exhibit diverse thermal gelation behavior. Gentz et al. teach the use of HPMC to increase the viscosity of the pharmaceutical compositions.

It appears that the Examiner has simply identified individual components in each of the Stratton et al. and Gentz et al. references, and then selectively extracted those individual components from the different contexts of those references and recombined the extracted components in yet another context that is asserted to render obvious the specific combination of the claimed hematopoietic growth factor delivery composition. The Examiner's position appears to be that any component disclosed for use in any drug delivery composition is combinable in any formulation combination with any other component disclosed for use in any other drug delivery composition. But such selective picking and choosing individual elements and combining those elements in a specific combination using the claimed invention as a guide is not proper.

Even considering solely for the sake of argument, however, that the teachings of Stratton et al. and Gentz et al. are properly combinable, such a hypothetical combination still would not render obvious the invention recited in Claim 1. For example, the Examiner cites to Gentz et al., column 2, lines 37-51 as disclosing polyoxyethylene-polyoxypropylene block copolymer and hydroxypropylmethyl cellulose. A review of this cited portion of Gentz et al., as well as other

portions of Gentz et al., reveals that Gentz et al. do not even disclose or suggest the use of polyoxyethylene-polyoxypropylene block copolymer and hydroxypropylmethyl cellulose together for delivery of even KGF-2 polypeptides, let alone for delivery of hematopoietic growth factors. Rather, Gentz et al. discloses only the separate use of HPMC and polyoxyethylene-polyoxypropylene block copolymers in alternative formulations for delivery of KGF-2 polypeptides. In the cited passage at column 2, lines 37-51, Gentz et al. specifically identify these alternative formulations as separate aspects of the invention, with one alternative formulation involving a "high molecular weight compound [e.g., polyoxyethylene-polyoxypropylene block copolymer] that causes the formulation to gel at a certain predefined temperature", and the other alternative formulation involving a "thickening agent" (e.g., HPMC) that is used "to increase the viscosity of the formulation".

Gentz et al. consistently treat polyoxyethylene-polyoxypropylene block copolymers and HPMC only as being used separately in these different alternative formulations, and do not disclose or suggest the use of polyoxyethylene-polyoxypropylene block copolymers in combination, let alone in the specific combination of the claimed invention involving a hematopoietic growth factor delivery composition. Gentz et al. specifically discuss thickened formulations at column 7, lines 49 through column 8, line 52. Gentz et al. then separately discuss gel formulations at column 8, lines 53 through column 10, line 61. The use of a thickening agent and the use of a gelling agent are clearly and consistently described by Gentz et al. only as formulation alternatives in delivery formulations specifically for KGF-2 polypeptides.

This consistency extends also to the examples provided by Gentz et al. at columns 28-32. Gentz et al. present examples showing formulations that include either a thickening agent or a gelling agent, but not both. Gentz et al. take care in describing the examples to distinguish thickened formulations from gel formulations. For example, Example 3 is specifically identified as a "Thickened Formulation" and includes the identified thickening agent carboxymethyl cellulose, but no polyoxyethylene-polyoxypropylene block copolymer. Conversely, Examples 4, 6 and 7 are each specifically identified as a "Gel Formulation", and each include pluronic F127 (a polyoxyethylene-polyoxypropylene block copolymer), but no thickening agent.

Moreover, Gentz et al. do not even discuss formulations for delivery of hematopoietic growth factors, and it is hard to imagine how the teachings of Gentz et al. involving alternative (but not combined) use of polyoxyethylene-polyoxypropylene block copolymer (for gel

formulations) or HPMC (for thickened formulations) for delivery of KGF-2 polypeptides (not hematopoietic growth factors) could possibly combine with the teaching of Stratton et al. to render obvious the claimed invention. Again, Claim 1 is directed very narrowly and specifically to a hematopoietic growth factor delivery composition including a first biocompatible polymer (such as for example a polyoxyethylene-polyoxypropylene block copolymer) and a liquid vehicle formulated to interact to impart specific reverse thermal viscosity behavior to the composition, a second biocompatible polymer (such as for example HPMC) that is a protective colloid inhibiting the dissolution into aqueous liquids of the first biocompatible polymer at least when the composition is in a higher viscosity form, and with specific compositional limitations wherein the liquid vehicle comprises from 60 weight percent to 96 weight percent the composition, the first biocompatible polymer comprises from 5 weight percent to 33 weight percent of the composition, and the second biocompatible polymer comprises from 0.1 weight percent to 5 weight percent of the composition. Clearly, neither Stratton et al. nor Gentz et al. (nor the combination of the two even if such a combination were proper) disclose or suggest the hematopoietic growth factor delivery composition of the invention as required of the specific combination of features recited in Claim 1, or in any claims that depend from Claim 1.

Rejection Under 35 U.S.C. § 103(a),
Based on Stratton et al. and Roos et al.

The Examiner has rejected Claims 27-32, 36 and 47 under 35 U.S.C. § 103(a) citing to Stratton et al. and Gentz et al., and in further view of Roos et al. (U.S. Patent No. 5,840,338). The rejection is traversed.

All of Claims 27-32, 36 and 47 ultimately depend from Claim 1, and therefore include all of the limitations of Claim 1. As discussed previously, Claim 1 is not obvious over Stratton et al. and Gentz et al. Claim 1 and the noted dependent claims are also not obvious over Stratton et al. and Gentz et al., further in view of and Roos et al.

As discussed above, Stratton et al. concerns a delivery system described as being generally applicable for delivery of macromolecular polypeptides, while Gentz et al. concerns specifically delivery formulations for delivery of the noted KGF-2 polypeptides. The teachings of Roos et al. concern loading of biologically active solutes (such as proteins, polypeptides, nuclear proteins, glycoproteins and lipoproteins) into polymer gels such that the biologically

active solutes loaded into the gels exhibit thermal and chemical stability, and more particularly the polymer gels discussed by Roos et al. are crosslinked polysaccharide gel networks. (See, Roos et al., for example, at column 1, lines 14-18, column 3, lines 10-14 and 54-55, column 6, lines 1-11, column 8, lines 23-26, column 13, line 46-48.).

The Examiner notes that Roos et al. refer to "PLURONIC®" polymers, HPMC, oral hepatitis B vaccine and granulocyte colony stimulating factor. The teachings of Roos et al., however, concern loading various drug molecules into crosslinked polysaccharide gel networks, which are disclosed by Roos et al. as being useful for delivery of the loaded drugs. Such crosslinked polysaccharide gel networks are significantly different from the claimed hematopoietic factor growth delivery composition, which includes a particular combination of components formulated in a particular way, and imparting specific reverse thermal viscosity behavior to the composition. Furthermore, the references made by Roos et al. to PLURONIC® polymers are not directed to the use of the PLURONIC® polymers to make reverse thermal viscosity formulations, but are rather directed to use of the PLURONIC® polymer as a "phase separating polymer" that is codissolved in a loading solution with the drug of interest for selectively partitioning, and thereby loading, the drug into the cross-linked polysaccharide gel network. (See, Roos et al., for example, at column 3, lines 31-40 and 54-61, and at column 8, lines 47-56.)

Clearly, Roos et al. do not disclose or suggest the very narrow and specific combination of features of the claimed hematopoietic growth factor delivery composition of Claim 1, which includes a first biocompatible polymer (such as for example a polyoxyethylene-polyoxypropylene block copolymer) and a liquid vehicle that interact to impart specific reverse thermal viscosity behavior to the composition, a second biocompatible polymer (such as for example HPMC) that is a protective colloid inhibiting the dissolution of aqueous liquids of the first biocompatible polymer at least when the composition is in a higher viscosity form, and with specific compositional limitations wherein the liquid vehicle comprises from 60 weight percent to 96 weight percent of the composition, the first biocompatible polymer comprises from 5 weight percent to 33 weight percent of the composition, and the second biocompatible polymer comprises from 0.1 weight percent to 5 weight percent of the composition.

Moreover, it is reiterated that the teachings of Stratton et al. are directed to a composition described as being generally applicable for suspensions of macromolecular polypeptides, while

the teachings of Gentz et al. concern delivery formulations specifically for delivery of the noted KGF-2 polypeptides. It is respectfully submitted that there is no teaching, suggestion or motivation for one of ordinary skill in the art to consider the teachings of Roos et al. (which concern loading drug solutes into cross-linked polysaccharide gel networks) in combination with the teachings of Stratton et al. (which concern delivery systems including suspensions of macromolecular polypeptides) or the teachings of Gentz et al. (which are directed to delivery formulations specifically only for KGF-2 polypeptides). Moreover, assuming solely for the sake of argument that such references are combinable, it is clear that such a combination would not disclose the specific combination of components formulated to provide the specific formulation properties for delivery specifically of hematopoietic growth factors.

Rejection Under 35 U.S.C. § 103(a),
Based on Stratton et al., Gentz et al. and Cha et al.

The Examiner has rejected Claims 2 and 3 under 35 U.S.C. § 103(a) citing to Stratton et al. and Gentz et al., and in further view of Cha et al. (U.S. Patent No. 5,702,717). The rejection is traversed.

As discussed above, neither Claim 1 nor any of the dependent claims are obvious over Stratton et al. and Gentz et al. Stratton et al. and Gentz et al. are each discussed above. The teachings of Cha et al. specifically concern preparation of thermosensitive biodegradable polymers and their use for parenternal administration of peptide and protein drugs, and in particular the use of thermosensitive biodegradable polymers based on poly (ether- ester) block copolymers. As noted by the Examiner, Cha et al. does provide a discussion concerning poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) tri-block polymers marketed under the "Pluronic™" tradename and concerning properties of selected formulations of some of the Pluronic™ polymers. The present invention, however, does not concern the discovery of any particular polymers or gelling properties of such Pluronic™ polymers, but rather concerns a specific combination of components formulated with specific features for delivery specifically of hematopoietic growth factors, with but one component of such specific combination being a first biocompatible polymer that in one embodiment may be a polyoxyethylene-polyoxypropylene block copolymer. There is no teaching, suggestion or motivation provided by Cha et al., either

alone or in any combination with Stratton et al. and Gentz et al., that would lead one of ordinary skill in the art to the very specific combination of elements recited in any of the pending claims.

It is respectfully submitted that all of the claim rejections based on 35 U.S.C. § 103(a) should be withdrawn.

It is believed that all of the issues raised in the Office Action have been addressed herein. Should the Examiner maintain any of the rejections of any of the pending claims, it is respectfully requested that it be pointed out with particularity how the cited reference(s) meet each and every term of each claim with respect to which rejection is maintained. In the absence of a persuasive showing to that effect, all pending claims should be allowed.

The application is believed to be in condition for allowance and allowance of all pending claims is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented herein, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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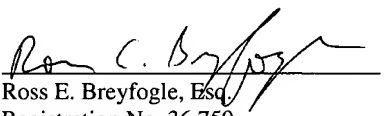
By: 

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